

EXHIBIT A

DEFENDANTS' DECEMBER 17, 2013
PROPOSED DISCOVERY SCHEDULE

Feb 5-6, 2014 – Science Days

April 30, 2014 -- Plaintiffs' Expert Report on Causation

May 30, 2014 – Deadline for agreement among the parties on the process for selecting Bellwether cases (Any unresolved issues could be submitted to the Court for decision within 20 days thereafter)

June 15, 2014 – Deadline for Deposition of Plaintiffs' Experts on Causation

June 27, 2014 – Deadline for selection of cases to comprise the Bellwether Discovery Pool

July 18, 2014 – Defendants' Expert Report on Causation

Aug 29, 2014 – Deadline for Deposition of Defendants' Experts on Causation

Sept 26, 2014 -- Daubert/SJ Motions on Causation

Oct 24, 2014 -- Responses to Daubert/SJ Motions

Nov 7, 2014 -- Replies to Daubert/SJ Responses

November, 2014 -- Daubert/SJ Hearing

December 15, 2014 – Close of all Generic and Bellwether Fact Discovery

January 6, 2015 – Selection of Cases for Bellwether Trials from Bellwether Pool

January 31, 2015 -- Plaintiffs' Expert Reports (other than on Causation issues previously addressed)

Feb 28, 2015 -- Defendants' Expert Reports (other than on previously addressed Causation issues)

Apr 18, 2015 -- Close of Expert Discovery

May 23, 2015 -- Daubert/ Dispositive Motions

July 18, 2015 -- Rule 26 (a) (3) PreTrial Disclosures

July 25, 2015 -- Meet and Confer on Final PreTrial Conference Order

August 1, 2015 -- Final PreTrial Conference Order

August 8, 2015 - Final PreTrial Conference

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UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF CALIFORNIA

IN RE: INCRETIN-BASED
THERAPIES PRODUCTS
LIABILITY LITIGATION

As to All Member Cases

Case No. 3:13-md-02452-AJB-MDD

MDL No. 2452

Judge: Hon. Anthony J. Battaglia
Magistrate: Hon. Mitchell D. Dembin

EXHIBIT B

**JANUVIA CLINICAL, OBSERVATIONAL AND PRECLINICAL DATA
SUMMARY**

1 The safety of Januvia has been established through randomized clinical trials,
2 observational database studies, and extensive animal (preclinical) testing. Of the
3 more than nearly 1,500 animals tested, none developed pancreatic cancer. And
4 across clinical trials involving thousands of individuals, and observational studies that
5 investigated Januvia treatment in tens of thousands of individuals, there was no
6 association between Januvia and pancreatic cancer.

7 **I. Randomized Clinical Trial Data**

8 Thousands of individuals have participated in randomized clinical trials of
9 Januvia. Based on its independent review of these studies, the EMA stated that the
10 Januvia clinical trial data “do not indicate a true association” between Januvia and
11 pancreatic cancer.¹ In addition, two publications from 2013 present these data and
12 address the question of causation directly.

13 The first—Samuel Engel et al., *Safety and Tolerability of Sitagliptin in Type 2*
14 *Diabetes: Pooled Analysis of 25 Clinical Studies*, Diab. Therapy (published online
15 May 23, 2013) (attached as Ex. 14)—is the largest patient-level data-set published to
16 date for any DPP-4 inhibitor. It pools all of the data from the randomized,
17 multicenter, double-blind clinical studies regarding Januvia (a total of 14,611
18 patients).² The pooled analysis of randomized clinical trials shows no increased risk
19 of pancreatic cancer. The data show that of the 7,726 patients treated with sitagliptin,
20 there were three incidents of pancreatic cancer (0.05 events per 100 patient-years),
21 and also three incidents in the 6,885 patients treated with comparator medications
22 (0.06 events per 100 patient years).

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25 ¹ EMA Report at 9 (Ex. 17).

26 ² A pooled analysis (or meta-analysis) has “the advantage of pooling more data so
27 that the results are less likely to be misleading solely due to chance.” *In re Bextra*,
28 524 F. Supp. 2d 1166, 1174 (N.D. Cal. 2007).

1 The second—Matteo Monami, *et al.*, *Dipeptidyl Peptidase-4 Inhibitors and*
2 *Pancreatitis Risk*, *Diabetes, Obesity & Metabolism*, 16:48–56 (published online July
3 9, 2013) (attached as Ex. 31)—also reveals no association between Januvia (and other
4 DPP-4 inhibitors) and pancreatic cancer. This meta-analysis combined data from 109
5 clinical trials involving more than 55,000 patients, including 43 Januvia trials and
6 over 10,000 patients taking Januvia, for a total exposure of over 45,000 patient years.
7 The data from this study showed that incidence rate of pancreatic cancer was the
8 same in patients using sitagliptin compared to patients using other medications. The
9 odds ratio was 0.72 (95% CI 0.32-1.61, $p = 0.42$).

10 **II. Observational Studies**

11 The observational data for Januvia also show no association with pancreatic
12 cancer. In 2013, a team of researchers published an observational database study that
13 included patients from all 50 states (a total of 72,738 users of oral antidiabetic drugs,
14 with 8,032 who used Januvia alone or in combination with other drugs).³ The authors
15 found no association between the use of Januvia and pancreatic cancer. They
16 concluded that the “observational data provide evidence of the comparative
17 effectiveness and safety of [Januvia] and support the recommendations in current
18 clinical practice guidelines to use sitagliptin as needed in people with diabetes.”⁴

19 A second study, presented at the June 2013 NIDDK/NCI conference on
20 pancreatic cancer and diabetes, presented data comparing the safety of DPP-4
21 inhibitors, including Januvia, to other diabetes treatments.⁵ The authors found no

22 ³ D. Eurich et al., *Comparative safety and effectiveness of sitagliptin in patients*
23 *with type 2 diabetes: retrospective population based cohort study*, *British Med. J.*,
24 346:f2267 (2013) (attached as Ex.16).

25 ⁴ *Id.* at 5.

26 ⁵ M. Gokhale et al., *Dipeptidyl Peptidase 4 Inhibitors and Comparative Pancreatic*
27 *Cancer Risk Among Older Adults*, Abstract presented at June 2013 NIDDK/NCI
28 conference (attached as Ex. 23).

1 increased risk of pancreatic cancer: compared to sulfonylureas, DPP-4 inhibitors had
2 an hazard ratio for pancreatic cancer of just 1.1 (95% CI, 0.6-1.8), and compared to
3 thiazolidinediones the hazard ratio was 0.50 (95% CI, 0.30–1.0).

4 **III. Preclinical (Animal) Data**

5 Merck conducted extensive animal studies of Januvia in multiple species at
6 exposures far exceeding human doses as part of the approval process.⁶ No animals in
7 the Januvia preclinical program developed pancreatic cancer, including animals in
8 two-year carcinogenicity studies exposed given Januvia at up to sixty-eight times the
9 human dose. In its recent report, the EMA stated that “no adverse effects on the
10 pancreas were observed” in these studies.⁷ In addition, two studies in diabetic
11 rodents published in 2013 found no evidence that Januvia causes adverse changes to
12 the pancreas.⁸ The EMA recognized that these findings are inconsistent with an
13 increased risk of pancreatic cancer.⁹

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15 Dated: February 10, 2014

Respectfully Submitted,

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19 ⁶ See Samuel Engel et al., *Sitagliptin: review of preclinical and clinical data*
20 *regarding incidence of pancreatitis*, Int’l J. of Clinical Practice, 64:984 (2010)
(attached as Ex. 15).

21 ⁷ EMA Report at 9 (Ex. 17).

22 ⁸ Thomas Forest et al., *Characterization of the Exocrine Pancreas in the Male*
23 *Zucker Diabetic Fatty Rat Model of Type 2 Diabetes Mellitus Following 3 Months*
24 *of Treatment with Sitagliptin*; Endocrinology (published online ahead of print Jan.
25 1, 2014) (attached as Ex. 20); K. Aston-Mourney et al., *One Year of Sitagliptin*
26 *Treatment Protects Against Islet Amyloid-associated β -cell Loss and Does Not*
27 *Induce Pancreatitis or Pancreatic Neoplasia in Mice*, Am. J. Physiology –
Endocrinology and Metabolism 305:E475–E484 (2013) (attached as Ex. 5).

28 ⁹ EMA Report at 9 (Ex. 17).

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UNITED STATES DISTRICT COURT
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IN RE: INCRETIN-BASED
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LIABILITY LITIGATION

As to All Member Cases

Case No. 3:13-md-02452-AJB-MDD

MDL No. 2452

Judge: Hon. Anthony J. Battaglia
Magistrate: Hon. Mitchell D. Dembin

EXHIBIT C

**VICTOZA CLINICAL, OBSERVATIONAL AND PRECLINICAL DATA
SUMMARY**

1 In January 2010, FDA approved Novo Nordisk's GLP-1 receptor agonist
2 Victoza (liraglutide) as an adjunct to diet and exercise to improve glycemic control in
3 adults with type 2 diabetes. Prior to approval, Novo Nordisk conducted an extensive
4 clinical development program to evaluate the safety and efficacy of Victoza. The
5 development program included both preclinical studies in mice, rats, and monkeys,
6 and more than 40 clinical trials in humans. FDA reviewed the totality of data
7 collected during the clinical development program and did not identify any issues
8 related to pancreatic cancer risk. On the contrary, in its Summary Review, FDA
9 stated that it did not find "a signal of malignancy in the [Victoza] database."¹ Since
10 Victoza came to market, Novo Nordisk has continued to study the pancreatic safety
11 of the medication in clinical trials, observational studies and animal studies.

12 **I. Randomized Clinical Trial Data**

13 As of June 2013, approximately 8,400 subjects have been treated with Victoza
14 in more than 50 clinical trials. In addition, Novo Nordisk is currently conducting the
15 LEADER trial, a large-scale cardiovascular safety trial in which more than 9,000
16 participants are being followed for up to five years at 410 sites in 32 countries.²
17 Incidence of cancer has been prospectively designated as a medical event of special
18 interest for evaluation in the trial, and all cases of pancreatic cancer are being
19 adjudicated by an event adjudication committee consisting of specialists in oncology
20 and endocrinology.³ An independent, external data-monitoring committee is

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22 ¹ See Victoza FDA Summary Review, Application 22-341 (January 25, 2013), at
23 14,
24 http://www.accessdata.fda.gov/drugsatfda_docs/nda/2010/022341s000TOC.cfm
(attached as Ex. 40).

25 ² Steven Marso et al., *Design of the liraglutide effect and action in diabetes:*
26 *Evaluation of cardiovascular outcome results (LEADER) trial*, Am. Heart J.
2013;166:823-830.e5, at 823 (attached as Ex. 29).

27 ³ *Id.* at 826, 830.e3.
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1 continually monitoring the safety of study participants and has authority to terminate
2 the trial if a safety issue arises.⁴ Results from the trial are expected in 2016-2017.
3 To date, no clinical trial has reported an increased risk of pancreatic cancer in patients
4 taking Victoza. Indeed, a recent review of the available clinical trial data conducted
5 by the European Medicines Agency found that “there is currently no support from
6 clinical trials that GLP-1 based therapies increase the risk” of pancreatic cancer.⁵

7 **II. Observational Studies**

8 Two large observational studies are currently underway to further evaluate the
9 safety of Victoza under real world treatment conditions, one in the United States
10 (OptumInsight) and the other in the United Kingdom (CPRD). Pancreatic cancer has
11 been prospectively identified as a medical event of special interest for evaluation in
12 both studies. Interim results from the OptumInsight study—reflecting more than
13 25,000 patient years of exposure to Victoza—were published in October 2013.⁶ The
14 authors found “no increased risk for [] pancreatic cancer in association with [Victoza]
15 treatment.”⁷ In fact, the rates of pancreatic cancer were lower in patients taking
16 Victoza than in those taking older diabetic medications, including metformin (RR
17 0.81, 95% CI 0.32-2.05) and sulfonylureas (RR 0.40, 95% CI 0.15-1.06).⁸ Final
18 results from both studies are expected in 2016-2017.

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21 ⁴ *Id.* at 826-27.

22 ⁵ EMA Report at 16 (Ex. 17).

23 ⁶ D. Funch et al., *A prospective, claims-based assessment of the risk of pancreatitis*
24 *and pancreatic cancer with liraglutide compared to other antidiabetic drugs*,
25 *Diabetes, Obesity and Metabolism* 2013; doi:10.1111/dom.12230 (attached as Ex.
26 21).

26 ⁷ *Id.* at 3.

27 ⁸ *Id.* at 2.

1 **III. Preclinical (Animal) Data**

2 The safety data set for Victoza includes studies conducted in nearly 2,000 rats,
3 mice, and monkeys, including two life-long carcinogenicity studies (involving more
4 than 1,100 animals) and a post-approval study in diabetic rats specifically designed to
5 evaluate the pancreatic effects of Victoza therapy.⁹ None of animals in these studies
6 developed pancreatic cancer—despite being treated with doses up to 60-times higher
7 than those used in humans—and none of the studies found evidence of treatment-
8 related adverse pathological effects on the pancreas. This preclinical data set was
9 reviewed by the European Medicines Agency in July 2013. The agency concluded
10 that “the non-clinical data do not indicate that [Victoza] treatment is associated with
11 adverse effects on the endocrine and exocrine pancreas.”¹⁰

12 Dated: February 10, 2014

13 Respectfully Submitted,

14 By: /s/ Loren H. Brown

15 Loren H. Brown
16 Raymond M. Williams
17 Heidi Levine
18 DLA PIPER LLP US

19 *Attorneys for Defendant Novo*
20 *Nordisk Inc.*

21

22 ⁹ Niels Nyborg et al., *The Human GLP-1 Analog Liraglutide and the Pancreas*
23 *Evidence for the Absence of Structural Pancreatic Changes in Three Species,*
24 *Diabetes* 2012;61:1243-1249 (attached as Ex. 34); Niels Vrang et al., *The effects*
25 *of 13 wk of liraglutide treatment on endocrine and exocrine pancreas in male and*
26 *female ZDF rats: a quantitative and qualitative analysis revealing no evidence of*
 drug-induced pancreatitis, *Am. J. Physiol. Endocrinol. Metab.* 2012;303: E253–
 E264 (attached as Ex. 41).

27 ¹⁰ EMA Report at 8 (Ex. 17).

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UNITED STATES DISTRICT COURT
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Case No. 3:13-md-02452-AJB-MDD

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Dembin

EXHIBIT D

**BYETTA CLINICAL, OBSERVATIONAL AND PRECLINICAL DATA
SUMMARY**

1 There are no scientifically reliable data demonstrating that Byetta is
2 associated with, much less capable of causing, pancreatic cancer. None of the most
3 reliable studies for testing hypotheses like those proposed by plaintiffs (randomized
4 clinical trials and controlled observational studies) has identified an increased risk
5 of pancreatic cancer associated with Byetta. Similarly, none of the animal studies
6 that have evaluated Byetta has found an increased rate of pancreatic cancer or
7 adverse pancreatic exocrine changes. In fact, none of the animals that have been
8 exposed to Byetta has developed pancreatic exocrine cancer.

9 **I. Randomized Clinical Trial Data**

10 No increased risk of pancreatic cancer was seen in the randomized clinical
11 trials for Byetta. Out of 4980 patients who participated in clinical trials for the
12 Byetta development program,¹ two Byetta-exposed patients and one insulin-
13 exposed patient developed pancreatic cancer.² The pancreatic cancer incidence
14 rates in the Byetta clinical trials were 0.07% (Byetta) vs. 0.13% (pooled
15 comparators), after accounting for differences in the length of time that patients
16 took these medications. In addition, randomized clinical trial data for Byetta was
17 evaluated in a 2012 meta-analysis that combined data from eight randomized
18 clinical trials. For purposes of evaluating cancer outcomes, the meta-analysis also
19 included data from two additional randomized clinical trials for the once-weekly
20 formulation of exenatide, known as Bydureon. Based on the combined data from
21 these ten Byetta and Bydureon clinical trials, the medications were not associated
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25 ¹ See Submission of Amylin Pharmaceuticals, Inc. to U.S. Food and Drug
26 Administration dated May 19, 2009 regarding Response to FDA Request for
Information (relevant pages attached as Ex. 3).

27 ² See Exenatide Periodic Safety Update Report for 01 October 2008 through
28 31 March 2009, dated May 20, 2009 (relevant pages attached as Ex. 19).

1 with a statistically significant risk of any cancer. (Specific types of cancer were not
2 evaluated in the analysis of all cancers.)³

3 **II. Observational Studies**

4 Three controlled observational studies, using four different databases,
5 different study designs, and evaluating over 60,000 Byetta-exposed patients, have
6 also found no statistically significantly increased risk⁴ of pancreatic cancer
7 associated with Byetta. Two of these studies have been published; another one has
8 been completed but is not yet published.⁵

9 **III. Nonclinical (Animal) Data**

10 Consistent with regulatory requirements for the evaluation of pharmaceutical
11 products, Byetta was evaluated in pre-approval animal studies. These studies were
12 conducted in more than 1600 mice, rats, and monkeys, for periods up to two years
13 and at doses substantially in excess of the human therapeutic dose. These studies
14 did not show pancreatic cancer or any drug-related effects from Byetta on the

16 ³ See Alves C, Batel-Marques F, Macedo AF. A meta-analysis of serious
17 adverse events reported with exenatide and liraglutide: acute pancreatitis and
cancer. *Diabetes Res Clin Pract.* 2012 Nov;98(2):271-84 (Ex. 2).

18 ⁴ The only human studies that purport to find an increased risk of pancreatic
19 cancer associated with Byetta are analyses of adverse event reports in the FDA's
AERS (Adverse Event Reporting System) database. See Elashoff M et al.
20 Pancreatitis, Pancreatic, and Thyroid Cancer with Glucagon-Like Peptide-1-Based
Therapy. *Gastroenterology*, 2011;141:150-156 (Ex. 13); Moore TJ et al.
21 QuarterWatch Monitoring MedWatch Reports. Perspectives on GLP-1 Agents for
Diabetes. ISMP, 2013;1-16 (Ex. 32). However, the authors of both studies
22 concluded that their analyses are only signal-generating and do not establish
causation.

23 ⁵ See Dore DD, et al. Incidence of Health Insurance Claims For Thyroid
24 Neoplasm and Pancreatic Malignancy in Association With Exenatide: Signal
Refinement Using Active Safety Surveillance. *Therapeutic Advances in Drug*
25 *Safety*. 2012;3(4):157-164 (Ex. 12); Romley JA, et al. Exenatide Therapy and the
Risk of Pancreatitis and Pancreatic Cancer in a Privately Insured Population.
26 *Diabetes Technol & Ther.* 2012;14(10):904-911 (Ex. 35); OptumInsight. Incidence
of Pancreatic Malignancy and Thyroid Neoplasm in Type 2 Diabetes Mellitus
27 Patients who Initiate Exenatide Compared to Other Antihyperglycemic Drugs.
Final Report. December 18, 2012.

1 exocrine pancreas⁶ – the location of the alleged cancers in this litigation.⁷ Two
2 other pre-approval animal studies were designed to evaluate whether Byetta might
3 cause cancer in rats and mice. These animals were exposed to doses of Byetta that
4 were much higher than the human therapeutic dosage. In addition, the animals
5 received Byetta for two years – a time equal to the animals' entire lifespan. These
6 two-year carcinogenicity studies did not detect any risk of pancreatic cancer with
7 Byetta.⁸ Further, a recent study in diabetic rodents found no evidence that Byetta
8 causes pancreatic cancer or any adverse changes to the pancreas.⁹

9 Dated: February 10, 2014

Respectfully Submitted,

11 RICHARD B. GOETZ
12 AMY J. LAURENDEAU
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13 By: /s/ Amy J. Laurendeau

14 Amy J. Laurendeau
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17 ⁶ Some animal studies have shown cellular changes (but no pancreatic
18 cancer) in the pancreases of rodents exposed to Byetta, but these results are not
19 supported by studies in humans. See Gier B et al. Chronic GLP-1 Receptor
Activation by Exentin-4 Induces Expansion of Pancreatic Duct Glands in Rats and
Accelerates Formation of Dysplastic Lesions and Chronic Pancreatitis in the
KRASG12D Mouse Model. *Diabetes*. 2012;61:1250-262 (Ex. 22).

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21 ⁷ See Tatarkiewicz K et al. Exenatide Does Not Evoke Pancreatitis and
Attenuates Chemically Induced Pancreatitis in Normal and Diabetic Rodents. *Am J*
Physiol Endocrinol Metab 2010;299:E1076-E1086, at E1082 (Ex. 38).

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23 ⁸ See Hiles R, et al. Exenatide Does not Cause Pancreatic Tumors or
Malignancies in Rats and Mice Following a 2-Year Period of Exposure. Presented
at 64th Scientific Session of the American Diabetes Association (2004), available at:
24 <http://professional.diabetes.org/Content/Posters/2004/p1585-P.pdf> (Ex. 26);
Tatarkiewicz K et al. Exenatide Does Not Evoke Pancreatitis and Attenuates
25 Chemically Induced Pancreatitis in Normal and Diabetic Rodents. *Am J Physiol*
Endocrinol Metab 2010;299:E1076-E1086, at E1082 (Ex. 39).

26
27 ⁹ See Tatarkiewicz K et al. No Evidence Of Drug-Induced Pancreatitis In Rats
Treated With Exenatide For 13 Weeks. *Diabetes Obes Metab*. 2013;15(5):417-26
28 (Ex. 38).

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